Trapping highly reactive dipolarophiles. Exploiting the mechanism associated with the azomethine ylide strategy for β-lactam synthesis

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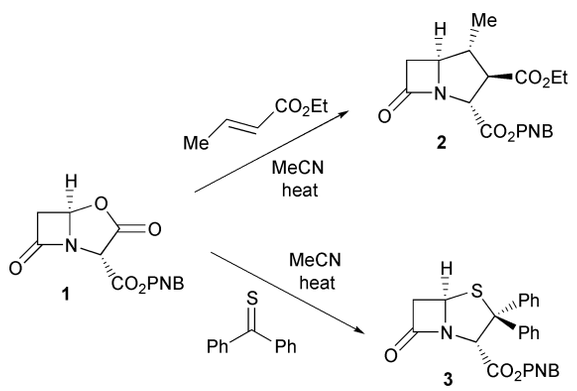
Highly reactive thioaldehydes **7**, which are generated transiently by thermolysis of thiosulfinates **6**, are trapped using azomethine ylide (derived from the β-lactam based oxazolidinone **1**) to give 2-substituted penams **8**. Diethyl thioxomalonate **10** and the selenoxo analogue **13**, both of which are generated transiently *via* a retro Diels–Alder reaction, undergo 1,3-dipolar cycloaddition reactions with **1** to give the isomeric penam **11a** and isopenam **11b**, and the 2,2-disubstituted selenapenam **14** respectively.

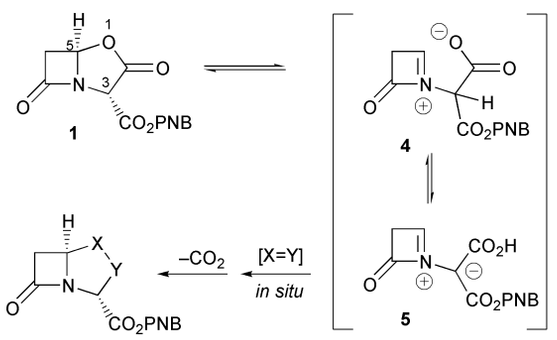
We have recently described a flexible and broadly applicable cycloaddition strategy for the synthesis of bicyclic β-lactams based on the generation and reactivity of azomethine ylides.[1] β-Lactam based *N*-acyloxazolidinones, such as **1**, are critical to this process and thermolysis of **1** in the presence of alkenes or thioketones provides direct access to carbapenams **2**[1a] and penams **3**[1b] respectively (Scheme 1).



Scheme 1 PNB = 4-nitrobenzyl.

N-Alkyloxazolidinones, which are readily prepared from α-amino acids and aldehydes, are known to provide azomethine ylides *via* a concerted and irreversible decarboxylation mechanism.[2,3] In contrast, evidence is now available to show that the β-lactam variants **1** (which are *N*-acyloxazolidinones) behave differently and undergo a *reversible* two-step fragmentation—C(5)–O(1) cleavage to give **4**, followed by proton tautomerisation ($CH \rightarrow OH$)—to release the key intermediate, the carboxylated azomethine ylide **5** (Scheme 2).[4]

To date, stable (isolable) 2π dipolarophiles (see Scheme 1) have served as viable traps for **5**. However, the equilibrium process shown in Scheme 2 makes it clear that the reactive azomethine ylide **5** is nevertheless "always present" and, as a consequence, constantly available for reaction. This unusual mechanistic property has now been exploited to capture a range of less conventional dipolarophiles. By this device, we have extended the scope of β-lactam-containing cycloadducts available. Specifically, our goal was to exploit highly reactive 2π



Scheme 2

components [X=Y], only available *via* generation *in situ*, and trap these entities with the crucial 1,3-dipole, azomethine ylide **5**, which is in equilibrium with the major tautomer oxazolidinone **1**. This concept is illustrated in Scheme 2.

Initial results were disappointing with efforts to trap benzyne using **5** failing to lead to a characterisable adduct. † Thioketones have, however, a proven utility in this area[1b] and with this in mind, we sought to trap the more elusive thioaldehydes **7**, which are available as described by Baldwin and Lopez[5] using thermal conditions suitable also for the generation of **5**. A solution of oxazolidinone **1** (present in excess) and a benzyl phenylmethanethiosulfinate (**6a** or **6b**) in MeCN was heated at reflux and following chromatography, the corresponding racemic 2-arylpenam **8a** and **8b** was isolated in 20 and 18% yield respectively, as shown in Scheme 3. ‡ The stereochemistry of cycloadducts **8a** and **8b** was assigned on the basis of ^{1}H and ^{13}C NMR and comparison of these data with those available from 2,2-disubstituted penams (*e.g.* **3**). Finally, the structure of **8a**

† To date we have failed to trap benzyne when benzenediazonium-2-carboxylate was heated in the presence of oxazolidinone **1**. Attempts to trap hexafluoroselenoacetone (generated from the corresponding anthracene cycloadduct[10] analogous to **12**) failed to give a characterizable product.

‡ Racemic cycloadducts are obtained from **1**, which is a consequence of the mechanism of formation of azomethine ylide **5**. Indeed, oxazolidinone **1** undergoes racemisation when heated in the absence of a dipolarophile.[4a,b]

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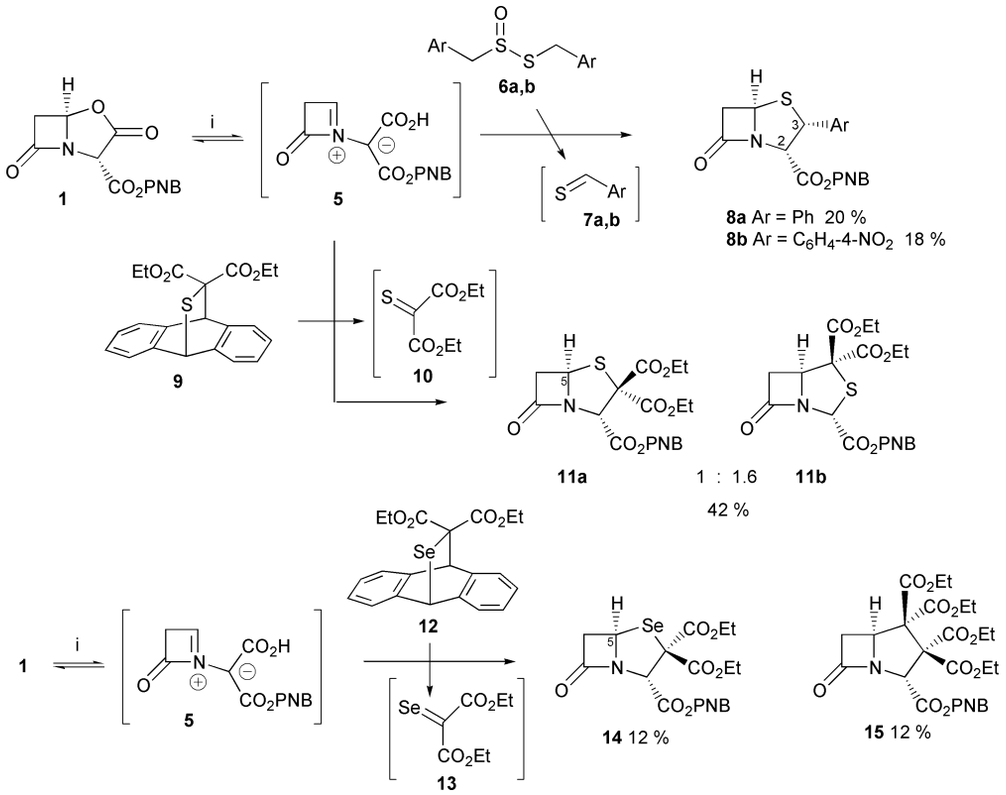


Scheme 3 *Conditions*: i, **1** and **6a** or **6b** (or **9** or **12**), MeCN, reflux.

was confirmed by X-ray crystallographic analysis (Fig. 1).§ In both cases, only a single isomer was observed and, based on crystallographic analysis and comparison of NMR data, the C(2)/C(3) stereochemistry of both **8a** and **8b** has been assigned as *cis*.¶

Diethyl 2-thioxomalonate **10** is available *via* a retro Diels–Alder reaction,[6] and thermolysis of the anthracene cycloadduct **9**[6] in the presence of an equimolar amount of oxazolidinone **1** gave an inseparable 1 : 1.6 mixture of the penam and isopenam[7] cycloadducts **11a** and **11b** respectively in a 42% combined yield. The assignment of the penam structure to the minor regioisomer **11a** is based on ^{1}H NMR data for H(5) (δ 5.37) compared to those observed for **8a** where H(5) appears at δ 5.56. In **11b**, H(5) appeared at δ 4.91.

Selenoketones form another group of highly reactive but rarely used dipolarophiles, though sterically hindered variants are isolable and have been trapped using the azomethine ylide strategy to provide a direct entry to selenapenams.[8] More reactive selenoketones can only be generated *in situ*, and thermolysis of the anthracene cycloadduct **12**[9] (to provide selone **13**) in the presence of oxazolidinone **1** gave the 2,2-disubstituted selenapenam **14** in 12% yield. The assignment of

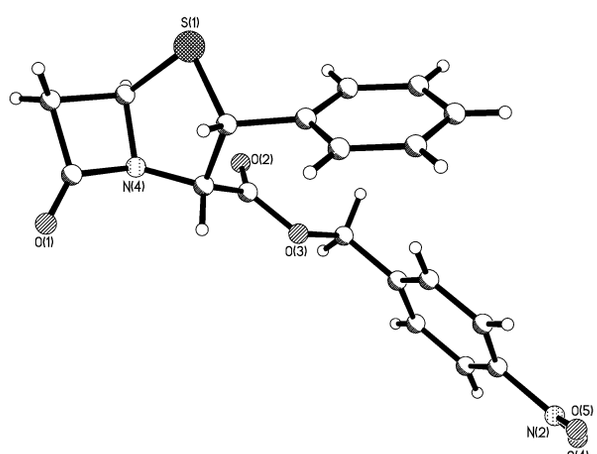


Fig. 1 Solid state structure of **8a**.

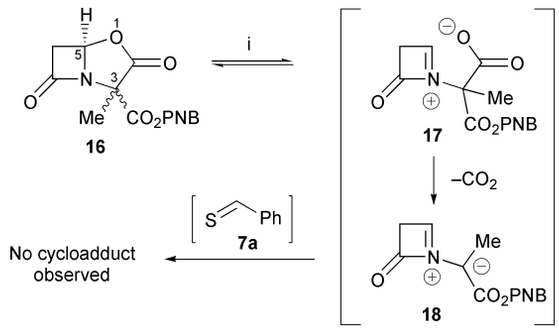
14 as a selenapenam (as opposed to an isoselenapenam) is based on the similarity of the NMR data derived from **11a** and **14** [H(5) appeared at δ 5.51], and is supported further by data available for related selenapenams.[8] Once again, the relative stereochemistry of C(2) and C(5) is based on the lack of a long-range (^5J) coupling between H(6α) and H(2).¶ The other significant product of this process, which reflects the high reactivity of selone **13**, was the carbapenam **15**, which was also obtained in 12% yield.‖

Further evidence for the requirement of a sustained steady-state concentration of the key 1,3-dipolar intermediate **5** in order to capture an elusive dipolarophile comes from attempts to trap thioaldehydes using the C(3) methylated oxazolidinone **16** (Scheme 4). This species has already been demonstrated to undergo a sequential ring opening [*via* cleavage of C(5)–O(1)] to give **17**, followed by an *irreversible* decarboxylation to release

§ Single crystals of **8a** were recrystallised from dichloromethane–petroleum ether, mounted in inert vacuum grease and transferred to the cold gas stream of the diffractometer. Crystal data: $C_{19}H_{16}N_2O_5S$, M = 384.40, monoclinic, a = 5.713(2), b = 31.81(12), c = 9.900(4) Å, β = 98.246(9)°, U = 1780.6(11) Å^3, T = 173 K, space group $P2_1/n$ (no. 14), Z = 4, μ(Mo-Kα) = 0.216 mm^{-1}, 9553 reflections measured, 3136 unique (R_{int} = 0.2446) which were used in all calculations. The final value of R_1 was 0.0707 [for 1275 reflections with $I > 2\sigma(I)$]. It should be noted that the crystal contains a racemic mixture of enantiomers due to the centrosymmetric nature of the space group. CCDC reference number 163810. See http://www.rsc.org/suppdata/p1/b1/b103271m/ for crystallographic files in .cif or other electronic format.

¶ The assignment of the *trans* (and thermodynamically more stable) relationship between H(2) and H(5) in **8a** and **8b** (and also **11a** and **11b**) is also based on the lack of a long-range (^5J) coupling between H(2) and H(6α). In the corresponding *cis* isomers, $^5J_{H(2)-H(6\alpha)} \approx 1$ Hz is observed.[7b,7g,11] Cycloadducts **14** and **15** also lack this long-range coupling.

‖ Tetraethyl ethylenetetracarboxylate is a known[9,12] by-product of the reaction used to generate **13**, and in a separate experiment thermolysis of **1** in the presence of this tetraester gave **15** in 23% yield.



Scheme 4 *Conditions*: i, **16** and **6a** in MeCN at reflux.

the reactive azomethine ylide **18**.[4b] However, thermolysis of **16** (as a mixture of diastereomers) in the presence of dibenzyl thiosulfinate **6a** failed to lead to a penam cycloadduct, and no β-lactam containing products derived from either **16** or **18** could be characterised. We attribute this result to the lack of a useful and sustained concentration of the reactive 1,3-dipole **18**, and the likely short lifetimes of both **7a** and **18** under these conditions.

While the yields of cycloadducts **8a**,**b**, **11** and **14** are only modest, the isolation and characterisation of these products do serve to underpin our current mechanistic stance. We have demonstrated an ability to trap transient, highly reactive dipolarophiles to provide a series of novel β-lactam structures. Although no information is yet available on the relative concentrations of oxazolidinone **1** *vs*. **4** *vs*. **5**, the observation that **5** will trap *in situ* generated dipolarophiles (such as **7a/b**, **10** and **13**) provides new experimental evidence for the general mechanistic hypothesis outlined in Scheme 2 concerning the fate of oxazolidinone **1** and the origins of azomethine ylide **5**. Further support for this hypothesis comes from our failure to capture a thioaldehyde with oxazolidinone **16**. Although this substrate undergoes a fragmentation to give a 1,3-dipole, this is an irreversible process that does not provide a sustained concentration of azomethine ylide **18**.

Experimental

General experimental procedures have recently been described.[4b] Proton and carbon assignments were made using a combination of ^{1}H/^{1}H and ^{1}H/^{13}C correlation spectroscopy.

General procedure for generation and trapping of thioaldehydes 7a and 7b

(±)-4-Nitrobenzyl (2*S,3*R**,5*R**)-7-oxo-3-phenyl-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 8a.** A solution of oxazolidinone **1** (34 mg, 0.11 mmol) and *S*-benzyl phenylmethanethiosulfinate **6a** (58 mg, 0.22 mmol) in CH_3CN (3.5 cm^3) was heated at reflux for 8 h (or alternatively at 100 °C in a sealed tube for 1 h), then evaporated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc) gave the *cis* diastereoisomer **8a** (17 mg, 20%) as a colourless solid. Mp 134–135 °C (dichloromethane–petroleum ether) (Found: $M^+ + H$, 385.0853. $C_{19}H_{17}N_2O_5S$ requires 385.0858); ν_{max} (CH_2Cl_2)/cm^{-1} 1782, 1751, 1609; δ_H (400 MHz, $CDCl_3$) 3.20 (1 H, dd, *J* 1.8, 16.0, 6α-H), 3.70 (1 H, dd, *J* 4.2, 16.0, 6β-H), 4.65 (1 H, d, *J* 13.0, CH_2Ar), 4.89 (1 H, d, *J* 13.0, CH_2Ar), 5.14 (1 H, d, *J* 7.5, C*H*), 5.35 (1 H, d, *J* 7.5, C*H*), 5.56 (1H, dd, *J* 1.8, 4.2, 5-H), 7.04 (2 H, part of AA′BB′, *J* 8.9, Ar), 7.24–7.29 (3 H, m, Ar), 7.38–7.41 (2 H, m, Ar), 8.10 (2 H, part of AA′BB′, *J* 8.9, Ar); δ_C (100.5 MHz, $CDCl_3$) 48.6 (CO*C*H$_2$), 60.9 (*C*H), 61.6 (*C*H), 65.4 (*C*H), 65.4 (Ar*C*H$_2$), 123.6 (*C*HAr), 128.4 (*C*HAr), 128.5 (*C*HAr), 128.7 (*C*HAr), 128.8 (*C*HAr), 134.1 (C*ipso*), 141.2 (C*ipso*), 148.5 (C*ipso*), 167.0 (C=O), 172.3 (C=O); *m*/*z* (CI) 385 ($M^{+\bullet} + H$, 4%).

(±)-4-Nitrobenzyl (2*S,3*R**,5*R**)-7-oxo-3-(4-nitrophenyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 8b.** Isolated as a colourless oil (Found: $M^+ + H$, 430.0714. $C_{19}H_{16}N_3O_7S$ requires 430.0709); ν_{max} (CH_2Cl_2)/cm^{-1} 1780, 1753; δ_H (300 MHz, $CDCl_3$) 3.23 (1 H, dd, *J* 1.6, 16.0, 6β-H), 3.77 (1 H, dd, *J* 4.3, 16.0, 6α-H), 4.73 (1 H, d, *J* 13.0, CH_2Ar), 4.92 (1 H, d, *J* 13.0, CH_2Ar), 5.21 (1 H, d, *J* 7.6, C*H*), 5.40 (1 H, d, *J* 7.6, C*H*), 5.58 (1 H, d d, *J* 1.6, 4.3, 5-H), 7.18 (2 H, part of AA′BB′, *J* 8.6, Ar), 7.54 (2 H, part of AA′BB′, *J* 8.6, Ar), 8.05 (2 H, part of AA′BB′, *J* 8.6, Ar), 8.13 (2 H, part of AA′BB′, *J* 8.6, Ar); *m*/*z* (CI) 430 ($M^{+\bullet} + H$, 10%).

(±)-4-Nitrobenzyl (2*S,5*R**)-7-oxo-3,3-bis(ethoxycarbonyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 11a and (±)-4-nitrobenzyl (2*S**,5*R**)-7-oxo-4,4-bis(ethoxycarbonyl)-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 11b.** A solution of oxazolidinone **1** (75 mg, 0.25 mmol) and anthracene cycloadduct **9**[6] (100 mg, 0.27 mmol) in MeCN (5 cm^3) was heated at reflux for 15 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (petroleum ether–EtOAc) to give an inseparable and 1 : 1.6 mixture of penam **11** and isopenam **11b** (45 mg, 42%) as a colourless oil (Found: $M^+ + H$, 452.0885. $C_{19}H_{20}N_2O_9S$ requires 452.0890); ν_{max} (CH_2Cl_2)/cm^{-1} 1780, 1749; δ_H (300 MHz, $CDCl_3$) 1.20 (3 H, t, *J* 7.1, Me, **11a**), 1.27 (3 H, t, *J* 7.1, Me, **11b**), 1.29 (3 H, t, *J* 7.1, Me, **11b**), 1.31 (3 H, t, *J* 7.1, Me, **11a**), 2.72 (1 H, dd, *J* 2.4, 16.5, 6β-H, **11b**), 3.20 (1 H, dd, *J* 2.0, 16.0, 6β-H, **11a**), 3.41 (1 H, dd, *J* 5.2, 16.5, 6α-H, **11b**), 3.57 (1 H, dd, *J* 4.0, 16.0, 6α-H, **11a**), 4.08–4.38 (8 H, m, 4 × CH_2, both isomers), 4.91 (1 H, dd, *J* 2.4, 5.2, 5-H, **11b**), 5.20–5.32 (4 H, m, 2 × CH_2, both isomers), 5.37 (1 H, dd, *J* 2.0, 4.0, 5-H, **11a**), 5.50 (1 H, s, 2-H, **11a**), 5.71 (1H, s, 2-H, **11b**), 7.53 (4 H, part of AA′BB′, *J* 8.6, both isomers, Ar), 8.25 (4 H, part of AA′BB′, *J* 8.6, both isomers, Ar); *m*/*z* (CI) 452 ($M^{+\bullet} + H$, 5%).

(±)-4-Nitrobenzyl (2*S,5*R**)-7-oxo-3,3-bis(ethoxycarbonyl)-4-selena-1-azabicyclo[3.2.0]heptane-2-carboxylate 14 and (±)-4-nitrobenzyl (2*R**,5*S**)-7-oxo-3,3,4,4-tetrakis(ethoxycarbonyl)-1-azabicyclo[3.2.0]heptane-2-carboxylate 15.** A solution of oxazolidinone **1** (200 mg, 0.65 mmol) and anthracene cycloadduct **12** (326 mg, 0.78 mmol) in MeCN (5 cm^3) was heated at reflux for 15 h in a sealed tube (in order to exclude O_2). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (petroleum ether–EtOAc) to give selenapenam **14** (36 mg, 12%) as a colourless oil (Found: M^+, 494.0398. $C_{19}H_{20}N_2O_9$74Se requires 494.0394); ν_{max} (CH_2Cl_2)/cm^{-1} 1788, 1754, 1603; δ_H (300 MHz, CD_2Cl_2) 1.08 (3 H, t, *J* 7.0, CH_3), 1.18 (3 H, t, *J* 7.0, CH_3), 3.16 (1 H, dd, *J* 16.0, 2.0, 6β-H), 3.59 (1 H, dd, *J* 16.0, 4.0, 6α-H), 3.92–4.23 (4 H, m, 2 × CH_2), 5.13 (1H, d, *J* 13.5, CH_2Ar), 5.19 (1 H, d, *J* 13.5, CH_2Ar), 5.41 (1 H, s, 3-H), 5.51 (1 H, dd, *J* 4.0, 2.0, 5-H), 7.58 (2 H, part of AA′BB′, *J* 9.0, Ar), 8.15 (2 H, part of AA′BB′, *J* 9.0, Ar); δ_C (75.5 MHz, CD_2Cl_2) 14.1 (*C*H$_3$), 14.2 (*C*H$_3$), 48.5 (6-*C*H$_2$), 57.3 (5-*C*H), 63.8 (*C*H$_2$), 64.0 (*C*H$_2$), 65.3 (3-*C*H), 66.7 (*C*H$_2$Ar), 124.3 (*C*H), 129.1 (*C*H), 142.7 (C*ipso*), 166.8 (C=O), 167.8 (C=O), 168.9 (C=O), 169.4 (C=O) (signals due to one Cquat. (2-C) and one C*ipso* were not observed); *m*/*z* (EI) (^{80}Se) 500 (M^+, 10%).

Continued elution gave carbapenam **15** (45 mg, 12%) as a colourless oil (Found: $M + H^+$, 579.1828. $C_{26}H_{31}N_2O_{13}$ requires 579.1826); ν_{max} (CH_2Cl_2)/cm^{-1} 1786, 1757; δ_H (300 MHz, $CDCl_3$) 1.21 (3 H, t, *J* 7.0, CH_3), 1.27 (3 H, t, *J* 7.0, CH_3), 1.28 (3 H, t, *J* 7.0, CH_3), 1.29 (3 H, t, *J* 7.0, CH_3), 2.66 (1 H, dd, *J* 16.5, 2.0, 6β-H), 3.41 (1 H, dd, *J* 16.5, 5.0, 6α-H), 4.04–4.35 (8 H, m, 4 × CH_2), 4.81 (1 H, dd, *J* 5.0, 2.0, 5-H), 5.23 (1 H, d, *J* 14.0, CH_2Ar), 5.33 (1 H, d, *J* 14.0, CH_2Ar), 5.40 (1 H, s, 2-H), 7.54 (2 H, part of AA′BB′, *J* 9.0, Ar), 8.23 (2 H, part of AA′BB′, *J* 9.0, Ar); δ_C (75.5 MHz, $CDCl_3$) 13.5 (*C*H$_3$), 13.7 (*C*H$_3$), 13.8 (*C*H$_3$), 13.9 (*C*H$_3$), 40.5 (6-*C*H$_2$), 58.8 (5-*C*H), 62.5 (*C*H$_2$), 62.8 (*C*H$_2$), 63.0 (*C*H$_2$), 63.2 (*C*H$_2$), 65.5 (2-*C*H),

65.9 (CH_2Ar), 65.9 (Cquat.), 69.0 (Cquat.), 123.8 (CH), 128.0 (CH), 142.4 (C*ipso*), 147.9 (C*ipso*), 166.3 (C=O), 166.9 (C=O), 167.1 (C=O), 167.5 (C=O), 168.1 (C=O), 171.8 (C=O).

In a separate experiment, thermolysis of **1** (MeCN, reflux, 24 h) in the presence of tetraethyl ethylenetetracarboxylate (1.1 equiv.) gave **15** in 23% yield.

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